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THE PERMEABILITY OF THE GASTRO-INTESTINAL WALL TO INFECTION WITH SPOROTHRIX SCHENCKII *

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The permeability of the mucosa of the gastro-intestinal tract to organisms of various kinds may be considered a phase of the general problem of focal infections.

Adami[1] years ago emphasized the constant passage of bacteria through apparently uninjured mucosa into the lymphatics and the blood stream. He showed that bacteria are found normally in various stages of disintegration especially in the lymph glands, spleen, and liver. He thought many of these organisms which appeared as diplococcoid forms were probably B. coli. Adami so well summarized his views based on his observations and on the reports in the literature at that time that I quote as follows:

"1. Normally there is a passage out of leukocytes through the mucosa on to the free surface of, more especially, the alimentary tract.

2. These leukocytes, while in part undergoing a destruction, in part find their way back between the epithelial cells, bearing with them foodstuffs and solid particles, among which may be the bacteria present in the cavity of the gut.

3. During the active congestion which accompanies digestion, the passage out and return of these wandering cells is increased.

4. These cells upon their return find their way either into the lymphatic channels or the venules of the portal system.

5. In either position, they tend to be destroyed and digested by the leukocytes and thus, while preparations of the mesentery and of the mesenteric lymphatic glands may show abundant bacteria, the vast majority of these at the same time show obvious degeneration, while cultures made from the mesentery or from the lymphatic glands upon ordinary media by ordinary methods as a consequence tend to remain sterile. Similarly in the normal liver, the same rapid destruction takes place, so that here again, by ordinary methods, no evidence of living bacteria is obtainable.

6. By the employment of adequate methods it can be demonstrated that even in the healthy liver and kidney in a large number of cases, in one animal at least—the rabbit—a certain number of living microbes are present at any one moment so that, if the healthy organ be removed from the body, cultures can be obtained of these living microbes.

7. It is most probable, that in ordinary health a certain number of bacteria which have not been destroyed by the leukocytes or removed by the lymphatic glands or endothelium of the portal system, pass either through the thoracic

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[1] Jour. Am. Med. Assn., 1899, 33, p. 1509.

duct or through the liver into the systemic blood. Such bacteria tend to be removed more especially by the kidneys, though it may be by other glandular organs. In any case the ordinary methods at present employed in making cultures from the blood are inadequate to detect the presence of such bacteria unless they are of such a nature or are circulating in such quantities that the whole number is not destroyed by the bactericidal power of the shed blood."

Adami here also discusses latent infections and the condition he calls subinfection, his views having a direct bearing on the general problem of focal infection as developed in more recent literature.

Indicative of the protective processes going on in the intestinal canal against invading organisms is the occurrence of certain types of inflammatory cells in the mucous membrane. At birth the pharyngeal and intestinal mucosa is sterile, but within the first 24-48 hours the canal becomes infected. For the first few days there are no inflammatory cells to speak of in the mucosa. Various types of such cells, especially plasma cells, then slowly appear in the mucosa and are always found thereafter. Such cells are especially numerous in certain parts of the alimentary canal, namely, the tonsils[2] and the appendix. No doubt one of the functions of such cells is that of protection against the infected intestinal contents, from which in accordance with the views of Adami and others bacteria are being absorbed.

In keeping with these observations is the fact that in new-born animals the permeability of the intestine is greater than in older animals. Von Behring[3] showed that ingested attenuated anthrax bacilli would infect new-born guinea-pigs, and Plate[4] reported that guinea-pigs 5 days old, when fed tubercle bacilli, developed tuberculosis whereas older guinea-pigs remained uninfected.

That bacteria pass through the apparently uninjured gastro-intestinal mucosa is a well-recognized fact experimentally. Ravenel infected guinea-pigs with chyle from dogs which a few hours previously had ingested tubercle bacilli with a large amount of fat.[5] Many workers have demonstrated that tubercle bacilli may pass through or between the epithelial cells and thence into the lymphatic glands and thoracic ducts without leaving any trace at the point of entry. It is true, however, that in order to obtain such experimental infections with tubercle bacilli enormous quantities must be ingested.

In this paper I wish to present certain experimental data bearing on the subject of the permeability of the alimentary mucosa to the

[2] Davis: Jour. Infect. Dis., 1912, 10, p. 142.

[3] Deutsch. med. Wchnschr., 1903, 29, p. 689.

[4] Inaugural Dissertation, 1905.

[5] Jour. Med. Research, 1904, 10, p. 460.

pathogenic organism Sporothrix schenckii. The experiments were designed, first, to test the permeability of the intestinal mucosa to a nonmotile organism many times larger than the bacteria which have been chiefly used heretofore in such experiments; second, to determine whether or not it is possible for sporotrichosis to be transmitted in this way from one animal or person to another.

The organism used was a typical Sporothrix schenckii isolated originally from a man living in North Dakota. The details of this case including a description of the organism have been reported by Hyde and Davis.[6]

The experiments were all made with the white rat because of its high susceptibility to infection with this organism when inoculated subcutaneously or intraperitoneally, and also because of its readiness to feed upon various preparations and media containing large numbers of these organisms. Young animals about three-fourths grown were used. They were kept in small compartment cages, always but one animal to a compartment to avoid, as far as possible, infection through bites and scratches.

As a routine the organisms were grown on agar-agar for about 10 days or 2 weeks. The growth, which as a rule is rather tough and leathery, was removed from the surface of the media, placed in a small mortar, and ground up. Later it was thoroughly mixed with from about 5 to 10 c.c. of milk. Mixing with other food was tried but milk was found to be the best vehicle. The rats readily consumed the organisms when thus prepared, especially if they had not been fed during the previous 12 hours.

Tests were made to determine the length of time the sporotricha remained alive in the stomach of the rat. At the end of 2 hours after the ingestion of the milk suspension, the spores and mycelium were always to be seen in the smears of the curdled milk, and by culture on suitable sugar media the organisms were readily recovered. At the end of 3 hours they could usually be recovered from the stomach. In the case of 4 rats, the stomach contents of which I examined at the end of 4 hours, I could not detect the organisms in smear or in culture. It should be pointed out that these observations were made on rats the stomachs of which were practically empty when the milk suspension was ingested.

A number of animals died within a short period of time following the feeding. Two different sets of 6 rats each died within from 24 to 48 hours after eating large quantities of cultures of the sporothrix. Occasionally in other sets of animals an individual would die. The stomach wall was in some instances red and the intestinal mucosa hyperemic. Examination of the heart blood and other body fluids did not reveal any sporothrix organisms. The young rats were more susceptible in this regard than the older animals. I suspect that they died from toxic substances derived from the organism or free in the cultures, but I am not sure that this is the true explanation of these rapid deaths. I am satisfied that they were not real sporothrix infections.

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[6] Jour. Cutan. Dis., 1910, 28, p. 321.

After eliminating a number of experiments which were unsatisfactory, I have observations on 13 animals which were fed cultures regularly over a period of several weeks or months. The data are summarized in Table 1. The amount of culture consumed by a rat in each feeding varied somewhat but was usually the growth from the surface of 1 agar slant, in some of the feedings one-half of this amount. It may be stated that this amount of growth when mixed in milk as described makes a fairly heavy suspension, a smear from which reveals in a single field hundreds of spores and many filaments.

TABLE 1

RESULTS OF FEEDING WHITE RATS WITH SPOROTHRIX SCHENCKII

Animal	Dates of Feeding	Number of Feedings	Period of Feeding	Date of Autopsy	Results
1	Apr. 29, May 12, 29	3	4 weeks	June 10	Negative
2	Apr. 29, May 12, 29	3	4 weeks	June 10	Negative
3	Apr. 29, May 12, 29	3	4 weeks	June 7	Positive
4	Apr. 29, May 12, 29	3	4 weeks	June 7	Positive
5	Sept. 26, Oct. 7, 20, Nov. 2, 4, 27, Dec. 8, 10, Jan. 20, 28	10	16 weeks	Feb. 24	Negative
6	Sept. 26, Oct. 7, 20, Nov. 2, 4, 27, Dec. 8, 10, Jan. 20, 28	10	16 weeks	Mar. 15	Negative
7	Sept. 26, Oct. 7, 20, Nov. 2, 4, 27, Dec. 8, 10, Jan. 20, 28	10	16 weeks	Mar. 23	Negative
8	Nov. 2, 3, 7	3	5 days	Nov. 16	Negative
9	Nov. 2, 3, 7, 27, Dec. 8, 10, Jan. 20, 28	8	11 weeks	Mar. 16	Negative
10	Nov. 2, 3, 7, 27, Dec. 8, 10, Jan. 20, 28	8	11 weeks	Feb. 24	Negative
11	Nov. 7, 27, Dec. 8, 10, Jan. 20, 28	6	10 weeks	Mar. 16	Negative
12	Nov. 7, 27, Dec. 8, 10, Jan. 20, 28	6	10 weeks	Mar. 18	Negative
13	Nov. 7, 27, Dec. 8, 10, Jan. 20	5	10 weeks	Feb. 16	Negative

Rats 3 and 4 on autopsy revealed definite and distinct lesions; these consisted of characteristic nodules in the omentum, the mesentery, and the lymph glands. The liver was not involved, tho lymph glands adjacent to it were. The spleen in one contained several nodes. Smears from these showed the typical elongated tissue forms, and cultures gave pure growths of the sporothrix. Infection of the lungs or thorax did not occur, nor any lesions of the skin.

A careful examination of the gastro-intestinal tract was made in every rat. In no instance were alterations, either active or healed, found in the gastro-intestinal mucosa or wall. It would appear, therefore, that at times the organisms pass through the intestinal mucosa without causing any appreciable local lesion, and localize in the neighboring lymph glands and other adjacent structures. In order to obtain further evidence on this point, I fed 6 very hungry rats with large quantities of the organisms in milk and at the end of from 2 to 4 hours killed the animals and made cultures of the heart blood and of the mesenteric and neighboring lymph glands. From this set of animals, however, all the culture tubes remained sterile indefinitely.

The organisms fed in these experiments were highly virulent for the rats. This had been determined a short time previously by inoculating a few drops of the suspension of the organisms into the peritoneal cavity or subcutaneously. Invariably infection occurred, terminating in a general and fatal infection in the course of a few weeks.

It is to be noted that the ingestion of large quantities of culture of the sporothrix is necessary in order to produce infection. As before stated, this is likewise true of the tubercle bacillus. When one considers the relative sizes of the two organisms it would seem reasonable to believe that the large spores of the sporothrix would pass through an intact epithelium with even far greater difficulty than would tubercle bacilli.

In this connection it may be mentioned that sporotricha are readily taken up by leukocytes both in vitro and in vivo. It is possible that the organisms were carried through the wall of the intestine by the migration of phagocytes. The recent work of Rous and Jones[7] showing the protective action of cells on intracellular organisms has a direct bearing on this point.

It has been shown by a number of observers that bacteria suspended in fat more readily pass through the mucosa into the chyle vessels than when fat is not present. It is possible that in the experiments here reported the fat in the milk played some rôle in the passage of the organisms through the mucous membrane of the rats. It is not contended however that this is the mechanism by which bacteria usually penetrate the intestinal wall. It may simply facilitate the process. M. Neisser[8] denies that bacteria penetrate the intestinal mucosa, his experiments on this point having proved completely negative.

Apparently no other experiments are recorded on this question of alimentary infection with Sporothrix schenckii. Gougerot[9] mentions having fed to rats and young guinea-pigs cultures of Sporothrix beurmanii. Two rats were fed with large amounts of such cultures for 6 months. Both animals became infected, and after 10 months one died and the other was killed. Extensive sporotrichotic lesions were found in both. Gougerot cites cases of pharyngeal sporotrichosis which he considers examples of infection with Sporothrix beurmanii through the mucous membrane. He mentions finding sporothrix organisms on the salad that the patient was eating, but is unable to say that the infection originated from this source.

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[7] Jour. Exper. Med., 1916, 23, p. 601.

[8] Ztschr. f. Hyg. u. Infektionskrankh., 1896, 22, p. 12.

[9] Bull. et mém. soc. méd. d. Hôp. de Paris, 1909, 27, p. 909.

As regards the bearing of clinical data on this subject, it is of course true that most cases of infection with Sporothrix schenckii result from injuries to the cutaneous surface. I do not know of any of the many cases of this infection now reported in this country in which the evidence indicates definitely that the atrium of infection was the gastro-intestinal tract. In cases of obscure origin this possibly should be considered.

SUMMARY

White rats fed at intervals of a few days with large quantities of cultures of Sporothrix schenckii may become infected.

The infection tends to localize in the mesentery, peritoneum, and spleen.

The organisms appear to penetrate the normal mucosa of the intestinal tract. No lesions active or healed were visible in the mucosa or in the wall of the stomach or intestines.